Applicants have amended claims 1, 4, 9, 11, 12 and 13. The amendments found support in the specification at page 5 and elsewhere. Thus, the changes are not new matter and are supported by the specification.

**35 U.S.C. § 112**

Claims 12-14 stand rejected for alleged indefiniteness. Specifically, the Examiner states that these are compound claims which improperly depend from method claims. As amended, however, claims 12-14 do not depend from method claims, and are entirely proper. The Examiner is therefor requested to reconsider and withdraw the rejection of these claims.

**35 U.S.C. § 102**

Claims 1, 2, 4 and 9 stand rejected as allegedly being anticipated by WO 96/33181 to Nakayama et al. (hereafter, the "'181 reference"). Applicants traverse these rejections. Each rejected claim has been amended and now recite methods wherein component "B" of the construct A-L-B is defined as on page 5 of the specification, lines 21-27 (i.e., "wherein substituents are independently lower alkyl, lower ankenyl, lower akkynyl, hydroxy, hydroxy-lower alkynyl, lower alkoxy, lower alkenyloxy, lower akenylenedioxy, lower alkanoyloxy, phenoxy, phenyl-lower alkoxy, acyl, carboxy, esterified carboxy, amidated carboxy, cyano, nitro, amino, acylamino, N-acyl-N-lower alkylamino, halo, halo-lower alkyl, and wherein phenyl, phenyl lower alkynyl, phenoxy, and phenyl lower-alkoxy are optionally substituted.).

In contrast to the present invention, the '181 reference requires that its $C_6$ aryl be substituted one of NHCO, CONH and $NHSO_2$ linked to C(O)OH or C(O)O-alkyl (i.e., A-$CH_2)_m$-G, where A is NHCO, CONH, or $NHSO_2$ and G comprises C(O)-hydroxy or –alkoxy). (See WO 96/33181, abstract and elsewhere.)

Claim 1 is directed to methods for modulating the activity of metabotropic glutamate receptors by contacting the receptors with compounds A-L-B. B is limited to the specific substituents recited above. Because of these amendments to B, the '181 reference does not "read on" A-L-B, and therefore cannot disclose methods of use of A-L-B. The same logic applies to the rejections of claims 2, 4 and 9. That is, the '181 reference does not disclose the A-

L-B structure according to these claims, and therefore cannot disclose the claimed methods for using A-L-B to treat disease or prevent pain.

Citation to methods disclosed in the '181 reference at pages 63-66 raises issues that are now moot. At most, disclosed on these pages are methods for using thiazol compounds expressly excluded from what is now claimed.

The Examiner's position as to inherent disclosure, i.e., that the '181 reference discloses compounds identical to those of claimed A-L-B compound, and thus would necessarily modulate the activity of metabotropic glutamate receptors and/or treat and prevent pain, is also now moot. Applicants do not believe that such an inherency position was warranted.[1] Nevertheless, inherency is no longer applicable here since A-L-B as recited in the amended claims is simply not disclosed in the '181 reference.

In sum, the '181 reference does not anticipate Claims 1, 2, 4 or 9 because it does not disclose the A-L-B of the amended claims or methods by which compounds A-L-B are used for any purpose. It is requested that the Examiner reconsider and withdraw the rejection of these claims under §102.

**35 U.S.C. §103**

Claims 1, 2, 4, 9 and 12 also stand rejected as allegedly being obvious over the '181 reference. Applicants traverse these rejections.

The rejections are based, at least in part, on the position that "the prior art discloses products and uses that contain the *same exact ingredients/components* as that of the claimed invention". This statement simply does not apply to the current claim set in light of the amendments to B. That is, the reference does not disclose the "same exact ingredients/components" as the instant invention.

Regarding claim 12, the Examiner merely alleged that one of ordinary skill in the art would have been motivated to use any of a number of salts, including toluene sulfonic salt, with the expectation that they would be pharmaceutically acceptable. Putting aside the issues of

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[1] See *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). ("To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, *and that it would be so recognized by persons of ordinary skill*") (emphasis added).

motivation to modify and reasonable expectation of success (discussed in Applicants previous response and incorporated by reference here), it is noted that, in light of the amendments to the claims, the issue no longer just the motivation to make a particular salt. It has now been made clear that the '181 reference discloses an entirely different compound. The Examiner has not suggested that the toluene sulfonic acid salt now claimed would be obvious. As discussed earlier, the '181 reference only discloses limited ethynylthiazole compounds where only ethynyl joins a thiazolyl to an aryl that must be linked to another extensive moiety, A-$(CH_2)_m$-G and methods of using such compounds as allergenic disease treating agents and leukotrine antagonist (p. 37 and claims 21-22). The '181 reference does not suggest modifying the compounds taught in the '181 reference, much less using such modified compounds to modulate the activity of metabotropic glutamate receptors or treat pain.

* * *

Applicants respectfully submit that the application is in condition for allowance and request a Notice of Allowance. If a telephone communication with Applicants' Attorney would be of assistance in handling this matter, please contact the undersigned attorney. Any fees required in connection with this submission may be taken from Merck Deposit Account No. 13-2755.

Respectfully submitted,

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Date: March , 2003

## CLAIMS MARKED-UP TO SHOW CHANGES

The brackets indicate deletion and underlines represent addition.

1. (Five Times Amended) A method of modulating the activity of metabotropic glutamate receptors, said method comprising:

contacting said receptors with at least one compound having the structure **A-L-B** or enantiomers, diastereomeric isomers or mixtures of any two or more thereof, or pharmaceutically acceptable salts thereof, in an amount sufficient to modulate the activity of metabotropic glutamate receptors wherein:

**A** is thiazolyl optionally substituted with 1 or 2 independent halogen, substituted or unsubstituted hydrocarbyl, substituted or unsubstituted aryl, heterocycle, mercapto, nitro, carboxyl, carbamate, carboxamide, hydroxy, ester, cyano, amine, amide, amidine, amido, sulfonyl or sulfonamide;

**L** is alkynylene; and

**B** is substituted or unsubstituted aryl,

wherein said aryl substituents are selected from lower alkyl, lower ankenyl, lower akkynyl, hydroxy, hydroxy-lower alkynyl, lower alkoxy, lower alkenyloxy, lower akenylenedioxy, lower alkanoyloxy, phenoxy, phenyl-lower alkoxy, acyl, carboxy, esterified carboxy, amidated carboxy, cyano, nitro, amino, acylamino, N-acyl-N-lower alkylamino, halo, halo-lower alkyl,

and wherein phenyl, phenyl lower alkynyl, phenoxy, and phenyl lower-alkoxy are optionally substituted.

4. (Five Times Amended) A method for treating a disease condition which is treatable by modulation of the activity of metabotropic glutamate receptors, said method comprising: administering to a patent having said disease condition, a therapeutically effective amount which is sufficient to modulate the activity of metabotropic glutamate receptors, of at least one compound having the structure **A-L-B** or enantiomers, diastereomeric isomers or mixtures of any two or more thereof, or pharmaceutically acceptable salts thereof, wherein:

**A** is thiazolyl optionally substituted with 1 or 2 independent halogen, substituted or unsubstituted hydrocarbyl, substituted or unsubstituted aryl, heterocycle, mercapto, nitro, carboxyl, carbamate, carboxamide, hydroxy, ester, cyano, amine, amide, amidine, amido, sulfonyl or sulfonamide;

**L** is alkynylene; and

**B** is substituted or unsubstituted aryl,

wherein said aryl substituents are selected from lower alkyl, lower ankenyl, lower akkynyl, hydroxy, hydroxy-lower alkynyl, lower alkoxy, lower alkenyloxy, lower akenylenedioxy, lower alkanoyloxy, phenoxy, phenyl-lower alkoxy, acyl, carboxy, esterified carboxy, amidated carboxy, cyano, nitro, amino, acylamino, N-acyl-N-lower alkylamino, halo, halo-lower alkyl,

and wherein phenyl, phenyl lower alkynyl, phenoxy, and phenyl lower-alkoxy are optionally substituted.

9. (Four Times Amended) A method for preventing pain in a subject at risk thereof, said method comprising: administering to a patent having said disease condition, a therapeutically effective amount which is sufficient to modulate the activity of metabotropic glutamate receptors, of at least one compound having the structure **A-L-B** or enantiomers, diastereomeric isomers or mixtures of any two or more thereof, or pharmaceutically acceptable salts thereof, wherein:

**A** is thiazolyl optionally substituted with 1 or 2 independent halogen, substituted or unsubstituted hydrocarbyl, substituted or unsubstituted aryl, heterocycle, mercapto, nitro, carboxyl, carbamate, carboxamide, hydroxy, ester, cyano, amine, amide, amidine, amido, sulfonyl or sulfonamide;

**L** is alkynylene; and

**B** is substituted or unsubstituted aryl,

wherein said aryl substituents are selected from lower alkyl, lower ankenyl, lower akkynyl, hydroxy, hydroxy-lower alkynyl, lower alkoxy, lower alkenyloxy, lower akenylenedioxy, lower alkanoyloxy, phenoxy, phenyl-lower alkoxy, acyl, carboxy, esterified carboxy, amidated carboxy, cyano, nitro, amino, acylamino, N-acyl-N-lower alkylamino, halo, halo-lower alkyl,

and wherein phenyl, phenyl lower alkynyl, phenoxy, and phenyl lower-alkoxy are optionally substituted.

11. (Four Times Amended) A pharmaceutically acceptable salt form of a compound, said compound having the formula A-L-B or enantiomers, diastereomeric isomers or mixtures of any two or more thereof, wherein:

**A** is thiazolyl optionally substituted with 1 or 2 independent halogen, substituted or unsubstituted hydrocarbyl, substituted or unsubstituted aryl, heterocycle, mercapto, nitro, carboxyl, carbamate, carboxamide, hydroxy, ester, cyano, amine, amide, amidine, amido, sulfonyl or sulfonamide;

**L** is alkynylene; and

**B** is substituted or unsubstituted aryl,

wherein said aryl substituents are selected from lower alkyl, lower ankenyl, lower akkynyl, hydroxy, hydroxy-lower alkynyl, lower alkoxy, lower alkenyloxy, lower akenylenedioxy, lower alkanoyloxy, phenoxy, phenyl-lower alkoxy, acyl, carboxy, esterified carboxy, amidated carboxy, cyano, nitro, amino, acylamino, N-acyl-N-lower alkylamino, halo, halo-lower alkyl,

and wherein phenyl, phenyl lower alkynyl, phenoxy, and phenyl lower-alkoxy are optionally substituted.

Claim 12. (Twice Amended) The pharmaceutically acceptable salt form of the compound [according to claim 1, wherein] **A-L-B**, wherein:

A is thiazolyl optionally substituted with 1 or 2 independent halogen, substituted or unsubstituted hydrocarbyl, substituted or unsubstituted aryl, heterocycle, mercapto, nitro, carboxyl, carbamate, carboxamide, hydroxy, ester, cyano, amine, amide, amidine, amido, sulfonyl or sulfonamide;

L is alkynylene; and

**B** is substituted or unsubstituted aryl,

wherein said aryl substituents are selected from lower alkyl, lower ankenyl, lower akkynyl, hydroxy, hydroxy-lower alkynyl, lower alkoxy, lower alkenyloxy, lower akenylenedioxy, lower alkanoyloxy, phenoxy, phenyl-lower alkoxy, acyl, carboxy,

esterified carboxy, amidated carboxy, cyano, nitro, amino, acylamino, N-acyl-N-lower alkylamino, halo, halo-lower alkyl,

and wherein phenyl, phenyl lower alkynyl, phenoxy, and phenyl lower-alkoxy are optionally substituted,

wherein the salt is a toluene sulfonic acid salt.

Claim 13. (Amended) The compound which is 2-methyl-4(phenyl ethynyl)-1,3-thiazole, and pharmaceutically acceptable salts thereof.